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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/012,904	01/23/1998	HARRY MEADE	TCI-028DV	2693

31904 7590 06/16/2004

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/012,904	MEADE ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 19, 21-23 and 25-30 are pending in the application.

This Office Action is in response to the Amendment filed on 3/10/04.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/10/04 has been entered.

Response to Amendment

The rejection of claims 19, 21-23 and 25-30 under 35 U.S.C.103 (a) is maintained for reasons set forth of the record mailed on 9/10/03 and further discussed below.

Claims 22, 28-30 are rejected under 35 U.S.C.112 1st paragraph for reasons discussed below.

Response to Arguments

Claims 19, 22, 23, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97).

In response to this rejection, Applicants argue that the cited reference fails to provide the desirability to combine the teaching to reach the claimed invention. Applicants further argue that Meade et al. fails to teach: I. expressing light chain and heavy chain of the immunoglobulin separately by using a mammary epithelial cell

comprising at least two vectors; II. a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin; III. use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk; IV a unique restriction site between promoter and the 3' non-coding sequence, wherein the immunoglobulin sequence is inserted into the restriction site; V. a unique restriction site in the construct; and VI. the advantage of having the unique restriction site within the construct. Applicants further argue that DeBoer et al. fails to teach these deficiencies. Moreover, Applicants assert that neither textual citation of DeBoer or the Figure cited in the previous office action demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted. Applicants thus conclude that the prior art does not render the invention obvious.

The above arguments has been fully considered but deemed unpersuasive. The claimed invention is obvious in view of the combined teaching of Meade et al. and DeBoer et al. for reasons discussed in detail in the previous office actions. The alleged deficiencies of I-III are not limitations of claims 19, 22, 23 and 25-28. Applicants are reminded although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). These claims do not recite the limitation of expressing light chain and heavy chain of the immunoglobulin separately. Contrary to Applicants' assertion that DeBoer et al. do not teach a unique restriction site in between a mammary gland promoter and 3' non-coding sequence, DeBoer et al. indeed teach such limitation. In response to Applicant's assertion that neither textual citation of DeBoer or the Figure

cited in the previous office action demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted, Applicants is reminded to read carefully of the cited text (Col.30, lines 45-50) and the figure (Figure 7E), the restriction site Xho I clearly lies in between the bovine αS1 casein promoter and the 3' non-coding region. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Since Meade et al. already teach a construct for expressing heterologous proteins including immunoglobulin (see col.3, lines 38-39) in mammalian milk, addition of a unique restriction site in between promoter and 3' non-coding region for addition of sequence encoding protein such as disclosed by DeBoer et al. is routine experimentation in the field of molecular cloning. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease recognition sites. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA

constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA into the vector without undue experimentation barring evidence to the contrary. Therefore, the claimed invention would have been obvious to one of ordinary skill of art at the time the invention was made.

Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., taken with DeBoer et al., (as applied to claims 19, 22, 23, and 25-28), in further view of Vandamme et al.

In response to this rejection, Applicants argue that the *in vitro* culture system taught by Vandamme et al. cannot serve as an accurate approximation of mammary gland milk synthesis of immunoglobulin assembly in whole animal. Particularly, Applicants assert that no one has established an *in vitro* system where the rates of synthesis of milk components proteins even closely approximate those found *in vivo*, hence, the two systems are incompatible and they are non-analogous art. Further Applicants assert that Vandamme references does not teach production of antibody in whole animal system, the physiological effect of lactation hormones, and milk promoters. Applicants thus conclude that the Vandamme reference teaches away from the methods required to achieve success in the expression of immunoglobulins of interest in the milk of transgenic animals.

Such arguments have been fully considered but deemed unpersuasive. Contrary to Applicants' assertion that Vadamme et al. is non-analogous art, Vadamme et al. is relevant to the claimed invention because it teaches production of recombinant immunoglobulin, which is within the field of the claimed invention, although the

production system may be different. This case is different from the Wang case discussed by Applicants in which the memory between the references and patents has different functions and are used in different context. Similarly, an apparatus in which film is transferred to a welding station and a tape-silencing machine capable of handling the same film are two different devices with distinct function. Therefore, the application of King and Wang case is irrelevant to the current situation. Although Vadamme et al. do not teach production of immunoglobulin in a whole animal system, the consideration of physiological effect of lactation hormones, milk promoters, such information is taught in the primary reference Meade et al. As a secondary reference, Vadamme et al. teach the construction of a recombinant murine monoclonal antibody directed against human fibrin fragment D by co-express plasmids comprising cDNA encoding immunoglobulin light chain and heavy chain separately. In response to applicant's arguments that the comparison of the instant invention and Vandamme is starkly different, Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). With combined teaching of Meade et al. and DeBoer et al., one of ordinary skill of art would have reasonable expectation of success to use a milk specific promoter and 3' non-coding sequence to replace the regulatory sequence taught by Vadamme et al. for preferential expression of the immunoglobulin in epithelial cell *in vivo*. The difference in the rate of synthesis between *in vitro* and *in vivo* is not relevant to the claimed invention because the claims do not recite such limitation. Therefore, claims 29 and 30 are obvious in view of cited references.

Claims 19, 21-23 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991).

In response to this rejection, Applicants argue that none of the references cited makes up for the deficiencies as discussed above. Applicants argue that the references do not knowingly suggest the combination of protocols, test, or principles that lead to the invention to be rendered obvious. Applicants thus conclude that the motivation for combining the references is based on hindsight reasoning.

The above arguments has been fully considered but deemed unpersuasive. As discussed in the previous office action and above, the combined teaching of Meade et al. and DeBoer et al. render claims 19, 22, 23, and 25-28 obvious. Therefore, no deficiencies has to be made up by the teaching of Bischoff et al., Buhler et al., Gordon et al., Ebert et al., and Stinnakre et al. for these claims. These references teach milk specific promoters that can be used in production of heterologous proteins in transgenic mammalian milk. Therefore, claim 21 is obvious because of combined teaching of Meade et al., DeBoer et al., in further view of Bishoff et al., Buhler et al., Gordon et al., Ebert et al. or Stinnakre et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, Applicants are again reminded that it must

be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. As such, the reference does not have to knowingly suggest the combination of protocols, test, or principles that lead to the invention to be rendered obvious, so long as the combined references provide motivation to combine and reasonable success to achieve the claimed invention. Such reasons for obviousness were discussed in detail in previous office actions. Therefore, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that

"as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims are drawn to a DNA construct or a cell comprising a DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal, wherein the immunoglobulin protein coding sequence encodes a light chain/heavy chain or "a fragment thereof." The claims encompass constructs encoding entire or portions of immunoglobulin of different size and/or structure. The specification does not teach portion(s)/fragment(s) of either light chain or heavy chain that would function as full length immunoglobulin. The specification also fails to teach any fragment of either light chain or heavy chain that can be assemble to be a biologically functional immunoglobulin. Furthermore, the specification fails to teach what structure these fragment(s) must share for them to function as a biologically active immunoglobulin. As such, the specification fails to disclose a representative number of the claimed fragments

by their complete structure or other identifying characteristics. Therefore, the written description requirement is not met.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.